Privileged and Confidential

May 10, 1994

Memorandum to Messrs. Bushong and Winokur

Re: IARC and Quantitative Estimation

We were asked at Friday's meeting to summarize what we know of an IARC paper dated March 1994 making recommendations regarding the agency's possible use of quantitative estimation and prediction ("QEP") methods with respect to cancer risks. This provides such a summary. I am sending it only to you, and leave any further distribution to your judgment.

1. Background. We understand that virtually every IARC working group has included members who want to use QEP to add specificity and punch to IARC's bland qualitative classification system. Our consultants believe that this probably explains the agency's decision to convene a working group to consider the issue. We are, however, continuing to explore the question, and it is by no means impossible that the report resulted from U.S. pressures.

2. The working group. A group of 23 was involved, including 10 from the U.S. The Americans included a representative of NCI, one from EPA, one from NIOSH, two from the National Institute of Environmental Health Sciences, and one from ILSI. There were 6 from the EU (including one from the Commission's environmental DG), plus one each from Sweden and Norway. The Norwegian is the country's most vehement anti-smoker, and a fervid user of quantitative estimates. There were two each from Australia and Canada, plus one Swiss. The Swiss was from WHO in Geneva. The chairman was one of the Australians, from the University of Adelaide. Putting aside ILSI, there was no one identifiable as from industry. There appear to have been no observers. Three others, all Americans, were invited but could not attend. They were all government-related, including another EPA representative. The secretariat list includes Boffetta, Tomatis and Vainio, among others.

3. IARC's use of QEP. The report begins with a description of IARC's general policy of avoiding QEP in the monograph series, which it largely attributes to uncertainties about QEP's reliability when the series was initiated. It notes that QEP involves a "a large judgmental component" which may significantly influence its results. The report observes, however, that IARC has contributed to QEP estimates outside the monograph series

(presumably in connection with WHO's QRP estimates), and claims that this is consistent with the agency's obligation to ascertain and present facts regarding risks in a fashion which will facilitate regulatory and other actions to prevent cancer. In other words, it attributes educational and policy functions to the agency.

4. The monograph series. The report provides a general description of the history and methods of the monograph system. It notes that human and animal data are first evaluated separately and then combined into an overall assessment. It also states that the monographs have been widely accepted as sound and dispassionate assessments, rigorously based upon science, and that they have made a "strong" contribution to regulatory decisions.

The report warns, however, that the monograph evaluations cannot be translated "directly" into policy, and that they should be only one relevant factor among many. Although those other factors were not specifically identified, a regulator could by implication use them to justify standards and limits even where a monograph assessment were cautious or unclear.

The report also notes that the monograph process has helped to resolve many of the uncertainties and doubts about QRP which existed when the series was begun. In addition, it states that, outside the monograph process, IARC has been conducting studies designed to permit quantitative estimates of the effects of low-dose exposures. ETS was not mentioned as one of the subjects of those studies. Overall, however, the group appeared to believe that the original reasons for avoiding QRP are now less forceful.

5. The value and methods of QRP. The report argues that quantitative estimates and predictions are important both scientifically and for purposes of public health policy. It distinguishes between "estimation," which is a direct application of existing data about exposure, and "prediction," which is an extrapolation to exposure levels about which data do not currently exist. "Estimations" are feasible from epidemiological or experimental data only in cases of relatively large risks. The report describes relative risks of 1.10 as the "usual" lower limit of detection in epidemiological studies, and states that at such levels "it can be difficult to rule out confounding and other biases." Although the report does not say so, presumably these difficulties would be multiplied in "predictions." Finally, the report acknowledges that QRP results must be accompanied by clear statements of their assumptions and weaknesses, and that they may sometimes be only tentative.

The report offers lengthy discussions both of the data needed for QRP and of the methods which may be used. Among other things, it acknowledges that extrapolations from high to low dose exposures

involve "uncertainty," encourages the identification of confounders and modifying factors, and states that physiologically-based pharmacokinetic modeling is "potentially" of great value in QRP. It states that accurate exposure data are "essential" for reliable QRP estimates, and that extrapolations between populations must be made with "caution."

6. <u>Recommendations</u>. The report recommends that the monograph series should not be altered, and that QRP should not be used in them, but urges the inclusion of more and better quantitative estimates and data. In other words, the monographs should do a better job of facilitating separate QRP estimates and predictions. Moreover, the report recommends that IARC should prepare QRP estimates for selected carcinogens about which extensive data are available, and publish them separately from the monograph series. No specific carcinogens were suggested for this purpose. It also recommends efforts to develop improved exposure measurements, including the use of biological markers, and the conduct of studies specifically designed to examine risks at low exposure levels. The report also encourages IARC to conduct scientific meetings and training programs regarding the proper use of QRP methods.

7. <u>Conclusions</u>. Unsurprisingly, the essence of the report is an encouragement to IARC to use QRP more widely and forcefully, and to facilitate its use by WHO and regulators. Given the frailities of the process, and its susceptibility to abuse, this is not good news. On the other hand, the report at least catalogs the weaknesses of QRP and encourages a greater and more consistent degree of professionalism and responsibility. Many of the warnings and caveats identified by the report (although not always highlighted) are precisely those we have long suggested.

We assume that the report will in due course be published (there is characteristically a delay of several months to a year), and, once it is, the report may be a useful source of evidence regarding the weaknesses and hazards of QRP.

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